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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/902,651	07/12/2001	Hiroyuki Nakane	77670/495	2816

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Judith L Toffenetti
Kenyon & Kenyon
1500 K Street NW
Suite 700
Washington, DC 20005

EXAMINER	
STEADMAN, DAVID J	

ART UNIT	PAPER NUMBER
1656	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	09/902,651	NAKANE ET AL.	
	Examiner	Art Unit	
	David J. Steadman	1656	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *29 June 2007*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-4,6,7,11-16 and 49-53* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-4,6,7,11-16 and 49-53* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *12 July 2001* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☒ Certified copies of the priority documents have been received in Application No. 08/898,560.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Status of the Application

[1] Claims 1-4, 6-7, 11-16, and 49-53 are pending in the application.

[2] Applicant's amendment to the claims, filed on 6/29/07, is acknowledged. This listing of the claims replaces all prior versions and listings of the claims. Applicant is reminded of the claim amendment practice according to 37 CFR 1.173(b)(2), which states, "[f]or any claim changed by the amendment paper, a parenthetical expression "amended, " "twice amended, " etc., should follow the claim number." It is noted that claims 49-53 appear to have been amended at least once and thus should have the proper parenthetical expression as noted above.

[3] Applicant's arguments filed on 6/29/07 in response to the Office action mailed on 2/6/07 are acknowledged. Applicant's arguments have been fully considered and are deemed to be persuasive to overcome some of the rejections and/or objections previously applied. Rejections and/or objections not reiterated from previous office actions are hereby withdrawn.

[4] The text of those sections of Title 35 U.S. Code not included in the instant action can be found in a prior Office action.

[5] In view of applicant's amendment to claim 1, the indicated allowability of claims 1, 11-13, 15, and 49-53 is withdrawn for reasons that follow. New rejections against claims 1, 11-13, 15, and 49-53 are set forth below.

Reissue Oath/Declaration

[6] Applicant is reminded of MPEP 1444.II, which states (in relevant part), "[a] supplemental oath/declaration need not be submitted with each amendment and additional correction. Rather, it is suggested that the reissue applicant wait until the case is in condition for allowance, and then submit a cumulative supplemental reissue oath/declaration pursuant to 37 CFR 1.175(b)(1). See MPEP § 1414.01 for a discussion of the required content of a supplemental reissue oath/declaration under 37 CFR 1.175(b)(1).

[7] The reissue oath/declaration filed with this application is defective (see 37 CFR 1.175 and MPEP § 1414) because of the following: the reissue Declaration states, "duty to disclose under 37 CFR 1.56(a)." However, the duty to disclose should be made under all sections of 37 CFR 1.56, not just 37 CFR 1.56(a). Appropriate correction is required.

Claim Objection

[8] Claim 6 is objected to in the recitation of "...a mutant enzyme of *Sulfolobus acidocaldarius.*" In order to improve the form of the claim, it is suggested that the noted phrase be amended to recite, "...a mutant of a *Sulfolobus acidocaldarius* prenyl diphosphate synthase."

[9] Claim 15 is objected to as being grammatically incorrect in the recitation of "...and of harvesting..." in the last line. It is suggested that the noted phrase be amended to recite, "...and harvesting..."

[10] Claims 1-4, 6-7, 11-16, and 49-53 are objected to as being based on a defective Oath/Declaration for the reason(s) set forth above.

[11] Claim 1 is objected to as not being modified from the original patent claim. See particularly claim 1 of US Patent 5,935,832, which states (in relevant part), "a modified amino acid sequence," in lines 1-2. Especially note the comma after "amino acid sequence." This comma is not present in claim 1 of the instant amendment. Appropriate correction is required. Applicant is requested to review the remaining amended claims to ensure that the amendments are made relative to the original patent claims.

Claim Rejections - 35 USC § 112, First Paragraph

[12] Claim(s) 1-4, 6-7, 11-16, and 49-53 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a written description rejection.

According to MPEP 2163.II.A.1, in evaluating a claimed invention for adequate written description, the examiner should determine what the claim as a whole covers. "Claim construction is an essential part of the examination process. Each claim must be separately analyzed and given its broadest reasonable interpretation in light of and consistent with the written description. See, e.g., *In re Morris*, 127 F.3d 1048, 1053-54, 44 USPQ2d 1023, 1027 (Fed. Cir. 1997)." As noted in the prior Office action, claim 1 as filed on 12/22/06 is limited to SEQ ID NO:1, except specifically recited mutations as set

forth in lines 4-14 of claim 1, *i.e.*, SEQ ID NO:1, except the mutations of T78F and H81A; except the mutations of T78F and H81L; except the mutations of F77Y, T78F, and H81L; except the mutations of F77Y, T78F, and H81A; or except the mutations of F77Y, T78S, V80I, I84L, and 84PS85, which is undisputed by applicant (Findings of the examiner which are not challenged are usually accepted as fact. *In re Kunzmann,* 326 F.2d 424, 140 USPQ 235 (CPA 1964)). Instant claim 1 has been amended to recite "[a] mutant prenyl diphosphate synthase having an amino acid sequence modified from the amino acid sequence of SEQ ID NO:1 by" the recited modifications. In accordance with MPEP 2163.II.A.1, the examiner has interpreted claim 1 as encompassing a genus of mutant prenyl diphosphate synthases, modified from SEQ ID NO:1 and having, in addition to the recited modifications, any additional modification(s) to SEQ ID NO:1. In other words, claim 1 has been interpreted as encompassing a genus of proteins that are modified from SEQ ID NO:1 having *at least* the modifications as recited in the claim, but not limited to those modifications. It is further noted the claim does not require the genus of mutants to maintain prenyl diphosphate synthase activity. In view of the amendment to claim 1, a written description rejection under 35 U.S.C. 112, first paragraph, is reinstated herein.

The Federal Circuit in *UC California v. Eli Lilly* (43 USPQ2d 1398) has said that a sufficient written description of a genus of DNAs may be achieved by a recitation of a representative number of DNAs defined by nucleotide sequence or a recitation of structural features common to members of the genus, which features constitute a substantial portion of the genus. For claims drawn to a genus, MPEP § 2163 states the

written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species by actual reduction to practice, reduction to drawings, or by disclosure of relevant, identifying characteristics, i.e., structure or other physical and/or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show the applicant was in possession of the claimed genus. MPEP § 2163 states that a representative number of species means that the species which are adequately described are representative of the entire genus. Thus, when there is substantial variation within the genus, one must describe a sufficient variety of species to reflect the variation within the genus.

In this case, the specification discloses five representative species of the claimed genus of mutant prenyl diphosphate synthase polypeptides, *i.e.,* Mutant enzyme 1: SEQ ID NO:1, except Thr78 is replaced with Phe and His81 is replaced with Ala; Mutant enzyme 2: SEQ ID NO:1, except Thr78 is replaced with Phe and His81 is replaced with Leu; Mutant enzyme 3: SEQ ID NO:1, except Phe77 is replaced with Tyr, Thr78 is replaced with Phe, and His81 is replaced with Leu; Mutant enzyme 4: SEQ ID NO:1, except Phe77 is replaced with Tyr, Thr78 is replaced with Phe, and His81 is replaced with Ala; Mutant enzyme 5: SEQ ID NO:1, except Phe77 is replaced with Tyr, Thr78 is replaced with Ser, Val80 is replaced with Ile, Ile84 is replaced with Leu, and an insertion of Pro-Ser between Ile84 and Met85, wherein all mutants have farnesyl diphosphate synthase enzyme activity. Other than these five representative species, the specification

fails to describe any additional representative species of the claimed genus of mutant polypeptides.

In this case, the genus encompasses all species of mutant prenyl diphosphate synthase polypeptides that are modified from SEQ ID NO:1, wherein the structures of the polypeptides are required only to have the minimal structural feature as recited in the claims, *i.e.,* Phe at position 78 and Ala at position 81; Phe at position 78 and Leu at position 81; Tyr at position 77, Phe at position 78, and Leu at position 81; Tyr at position 77, Phe at position 78, and Ala at position 81; and Tyr at position 77, Ser at position 78, Ile at position 80, Leu at position 84, and inserting Pro-Ser between positions 84 and 85. The mutant can have any other alteration(s) outside of these amino acid positions. While it is acknowledged that the noted structural features are common to all members of the genus, they do not constitute a substantial portion of the genus as the remainder of the structure of the polypeptide is completely undefined. Further, as noted above, the members of the genus are not required to have prenyl diphosphate synthase enzymatic activity. As such, the genus of mutant prenyl diphosphate synthase polypeptides can have any activity, including polypeptides that are non-functional and polypeptides that have an activity that is distinct to that of prenyl diphosphate synthase. Thus, it is the examiner's position that the five disclosed representative species fail to reflect the variation among the members of the genus, which encompass widely variant species with respect to both structure and function.

Given the lack of description of a representative number of polypeptides, the specification fails to sufficiently describe the claimed invention in such full, clear,

concise, and exact terms that a skilled artisan would recognize that applicant was in possession of the claimed invention.

[13] Claims 1-4, 6-7, 11-16, and 49-53 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for Mutant enzyme 1: SEQ ID NO:1, except Thr78 is replaced with Phe and His81 is replaced with Ala; Mutant enzyme 2: SEQ ID NO:1, except Thr78 is replaced with Phe and His81 is replaced with Leu; Mutant enzyme 3: SEQ ID NO:1, except Phe77 is replaced with Tyr, Thr78 is replaced with Phe, and His81 is replaced with Leu; Mutant enzyme 4: SEQ ID NO:1, except Phe77 is replaced with Tyr, Thr78 is replaced with Phe, and His81 is replaced with Ala; Mutant enzyme 5: SEQ ID NO:1, except Phe77 is replaced with Tyr, Thr78 is replaced with Ser, Val80 is replaced with Ile, Ile84 is replaced with Leu, and an insertion of Pro-Ser between Ile84 and Met85, wherein all mutants have farnesyl diphosphate synthase enzyme activity, does not reasonably provide enablement for *all* mutant prenyl diphosphate synthases as broadly encompassed by the claims.

The test of enablement is not whether any experimentation is necessary, but whether, if experimentation is necessary, it is undue." *In re Angstadt*, 537 F.2d 498, 504, 190 USPQ 214, 219 (CCPA 1976). Factors to be considered in determining whether undue experimentation is required are summarized in *In re Wands* (858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988)) as follows: (A) The breadth of the claims; (B) The nature of the invention; (C) The state of the prior art; (D) The level of one of ordinary skill; (E) The level of predictability in the art; (F) The amount of direction

provided by the inventor; (G) The existence of working examples; and (H) The quantity of experimentation needed to make or use the invention based on the content of the disclosure. See MPEP § 2164.01(a). MPEP 2164.04 states, "[w]hile the analysis and conclusion of a lack of enablement are based on the factors discussed in MPEP § 2164.01(a) and the evidence as a whole, it is not necessary to discuss each factor in the written enablement rejection" and that "[t]he language should focus on those factors, reasons, and evidence that lead the examiner to conclude that the specification fails to teach how to make and use the claimed invention without undue experimentation, or that the scope of any enablement provided to one skilled in the art is not commensurate with the scope of protection sought by the claims." Accordingly, the Factors most relevant to the instant rejection are addressed in detail below.

The breadth of the claims: According to MPEP 2164.04, "[b]efore any analysis of enablement can occur, it is necessary for the examiner to construe the claims...and explicitly set forth the scope of the claim when writing an Office action." Also, MPEP 2164.08 states, "[a]ll questions of enablement are evaluated against the claimed subject matter. The focus of the examination inquiry is whether everything within the scope of the claim is enabled. Accordingly, the first analytical step requires that the examiner determine exactly what subject matter is encompassed by the claims" (citation omitted) and "[w]hen analyzing the enabled scope of a claim, the teachings of the specification must not be ignored because claims are to be given their broadest reasonable interpretation that is consistent with the specification." As noted above, in the prior Office action claim 1 as filed on 12/22/06 is limited to SEQ ID NO:1, except specifically

recited mutations as set forth in lines 4-14 of claim 1, *i.e.,* SEQ ID NO:1, except the mutations of T78F and H81A; except the mutations of T78F and H81L; except the mutations of F77Y, T78F, and H81L; except the mutations of F77Y, T78F, and H81A; or except the mutations of F77Y, T78S, V80I, I84L, and 84PS85, which is undisputed by applicant. Instant claim 1 has been amended to recite "[a] mutant prenyl diphosphate synthase having an amino acid sequence modified from the amino acid sequence of SEQ ID NO:1 by" the recited modifications. In accordance with MPEP 2164.08, the examiner has broadly, but reasonably interpreted claim 1 as encompassing all mutant prenyl diphosphate synthases, modified from SEQ ID NO:1 and having, in addition to the recited modifications, any additional modification(s) to SEQ ID NO:1. In other words, claim 1 has been interpreted as encompassing all proteins that are modified from SEQ ID NO:1 having *at least* the modifications as recited in the claim, but not limited to those modifications. It is further noted the claim does not require the claimed mutant polypeptide to maintain prenyl diphosphate synthase activity. In view of the amendment to claim 1, a scope of enablement rejection under 35 U.S.C. 112, first paragraph, is reinstated herein.

The state of the prior art; The level of one of ordinary skill; and The level of predictability in the art: The amino acid sequence of a polypeptide determines its structural and functional properties. Predictability of which changes can be tolerated in a protein's amino acid sequence and obtain the desired activity requires a knowledge of and guidance with regard to which amino acids in the protein's sequence, if any, are tolerant of modification and which are conserved (*i.e.,* expectedly intolerant to

modification), and detailed knowledge of the ways in which the protein's structure relates to its function. The positions within a protein's sequence where modifications can be made with a reasonable expectation of success in obtaining an encoded polypeptide having the desired activity/utility are limited in any protein and the result of such modifications is highly unpredictable. In addition, one skilled in the art would expect any tolerance to modification for a given protein to diminish with each further and additional modification, *e.g.,* multiple substitutions. In this case, the necessary guidance has not been provided in the specification as explained in detail above. Thus, a skilled artisan would recognize the high level of unpredictability associated with altering the amino acid sequence of a polypeptide.

The state of the art provides evidence for the high degree of unpredictability in altering a polypeptide sequence with an expectation that the altered polypeptide will have the desired activity/utility. For example, Branden et al. ("Introduction to Protein Structure", Garland Publishing Inc., New York, 1991; cited in a prior Office action) teach "[p]rotein engineers frequently have been surprised by the range of effects caused by single mutations that they hoped would change only one specific and simple property in enzymes" and "[t]he often surprising results of such experiments reveal how little we know about the rules of protein stability... ...they also serve to emphasize how difficult it is to design *de novo* stable proteins with specific functions" (page 247). Witkowski et al. (*Biochemistry* 38:11643-11650, 1999; cited in a prior Office action) exemplify the teachings of Branden et al. by disclosing that a single amino acid substitution results in conversion of the parent polypeptide's activity from a beta-ketoacyl synthase to a

malonyl decarboxylase (see e.g., Table 1, page 11647). The reference of Ohnuma et al. (*J. Biol Chem* 271:10087-10095; cited in the IDS filed October 21, 1997, Paper No. 8, of application 08/898,560). Applicants do not dispute that Ohnuma et al. teach a *B. stearothermophilus* geranylgeranyl diphosphate synthase having a mutation at the fifth amino acid (Tyr81) upstream of Asp86 of the acid-rich domain and acknowledge the mutant of Ohnuma et al. catalyzes the biosynthesis of a product that is *longer* than the substrate (see page 4 of Paper No. 13, filed August 07, 1998 of application 08/898,560). See also MPEP 2144.08.II.A.4.(c), which states, "[t]he effect of a conservative substitution on protein function depends on the nature of the substitution and its location in the chain. Although at some locations a conservative substitution may be benign, in some proteins only one amino acid is allowed at a given position. For example, the gain or loss of even one methyl group can destabilize the structure if close packing is required in the interior of domains. James Darnell *et al., Molecular Cell Biology* 51(2d ed. 1990)." Thus, the prior art acknowledges the unpredictability of altering a protein-encoding sequence with an expectation of obtaining a protein having a desired function and discloses that even a single substitution in a polypeptide's amino acid sequence may completely alter the function of a polypeptide.

The amount of direction provided by the inventor and The existence of working examples: The specification discloses only five working examples encompassed by the scope of the claimed polypeptides, *i.e.,* Mutant enzyme 1: SEQ ID NO:1, except Thr78 is replaced with Phe and His81 is replaced with Ala; Mutant enzyme 2: SEQ ID NO:1, except Thr78 is replaced with Phe and His81 is replaced with Leu; Mutant enzyme 3:

SEQ ID NO:1, except Phe77 is replaced with Tyr, Thr78 is replaced with Phe, and His81 is replaced with Leu; Mutant enzyme 4: SEQ ID NO:1, except Phe77 is replaced with Tyr, Thr78 is replaced with Phe, and His81 is replaced with Ala; Mutant enzyme 5: SEQ ID NO:1, except Phe77 is replaced with Tyr, Thr78 is replaced with Ser, Val80 is replaced with Ile, Ile84 is replaced with Leu, and an insertion of Pro-Ser between Ile84 and Met85, wherein all mutants have farnesyl diphosphate synthase enzyme activity. While methods for altering a polypeptide's sequence were known in the art at the time of the invention, the teachings provided by the specification and prior art fail to provide the necessary guidance for making and using the entire scope of claimed polypeptides. For example, the specification fails to provide guidance regarding those amino acids of SEQ ID NO:1 that may be altered by substitution, insertion, addition and/or deletion with an expectation of maintaining the desired biological activity. Moreover, the specification fails to provide any guidance for using those mutant enzymes as encompassed by the claims that do not maintain farnesyl diphosphate synthase enzymatic activity.

The quantity of experimentation needed to make or use the invention based on the content of the disclosure: While methods of generating variants of a given polypeptide are known in the art, *e.g.,* mutagenesis, it is not routine in the art to screen for *all* polypeptides having a substantial number of substitutions or modifications as encompassed by the instant claims for those that have the ability to synthesize prenyl diphosphate.

Thus, in view of the overly broad scope of the claims, the lack of guidance and working examples provided in the specification, the high level of unpredictability as

evidenced by the prior art, and the amount of experimentation that is required, undue experimentation would be necessary for a skilled artisan to make and use the entire scope of the claimed invention. Thus, applicant has not provided sufficient guidance to enable one of ordinary skill in the art to make and use the claimed invention in a manner reasonably correlated with the scope of the claims. The scope of the claims must bear a reasonable correlation with the scope of enablement (*In re Fisher*, 166 USPQ 19 24 (CCPA 1970)). Without sufficient guidance, determination of having the desired characteristics is unpredictable and the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue. See *In re Wands* 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988).

[14] The new matter rejection of claims 2 and 16 under 35 U.S.C. 112, first paragraph, is maintained for the reasons of record and the reasons stated below. The rejection was fully explained in prior Office actions.

RESPONSE TO ARGUMENT: Beginning at the middle of page 14 of the instant remarks, applicant argues the recited limitation of "synthesizes more farnesyl diphosphate than the amount of farnesyl diphosphate synthesized by the wild type prenyl diphosphate synthase under similar conditions" in claim 2 (claim 16 dependent therefrom) is supported by Figure 3 and thus the limitation is not new matter.

Applicant's argument is not found persuasive. While Figure 3 may provide inherent support for the limitation of synthesizing more farnesyl diphosphate than the amount of farnesyl diphosphate synthesized by the wild type prenyl diphosphate

synthase under *identical* conditions as set forth at Example 5 (columns 12-14) for those specific mutants as disclosed in Figure 3 of the specification, the Figure would not appear to support a limitation of synthesizing more farnesyl diphosphate than the amount of farnesyl diphosphate synthesized by the wild type prenyl diphosphate synthase under *similar* conditions, particularly where the conditions are those other than the conditions set forth at Example 5 of the specification, for all mutants as encompassed by the claims. In this case, Figure 3 would not appear to provide express, inherent, or implicit disclosure for comparing the amount of farnesyl diphosphate synthase synthesized by all mutants as encompassed by the claims and wild-type enzymes of Figure 3 under conditions that may be similar, but are not identical. Further, Figure 3 would not appear to provide any express, inherent, or implicit disclosure for comparing the amount of farnesyl diphosphate synthase synthesized by the mutant and wild-type enzymes under any conditions other than those as set forth at Example 5 of the specification.

Applicant is invited to show support for the limitation at issue.

[15] The new matter rejection of claim(s) 7 and 16 under 35 U.S.C. 112, first paragraph, is maintained for the reasons of record and the reasons stated below. The rejection was fully explained in prior Office actions.

RESPONSE TO ARGUMENT: Beginning at the bottom of page 14 of the instant remarks, applicant argues the recited limitation of "having a higher enzymatic activity using isopentenyl diphosphate as a substrate at a temperature of 80 °C than that of the

wild-type prenyl diphosphate synthase" in claim 7 (claim 16 dependent therefrom) is supported by Figure 2 and the disclosure at column 13, lines 1-14. According to applicant, in view of this disclosure the limitation is not new matter.

Applicant's argument is not found persuasive. While Figure 2 and the disclosure at column 13, lines 1-14 may provide inherent support for the limitation of the mutants of Figure 2 having a higher relative activity using isopentenyl diphosphate as a substrate at a temperature of 80 °C and under identical conditions as set forth at Example 5 of the specification than that of the wild-type prenyl diphosphate synthase, Figure 2 and the disclosure at column 13, lines 1-14 would not appear to provide any express, inherent, or implicit support for the noted limitation.

Applicant is invited to show support for the limitation at issue.

Examiner Comment/Clarification

[16] In the prior Office action, the examiner asserted that the mutant enzyme of claim 1 synthesizes prenyl diphosphate that is shorter than the prenyl diphosphate of the corresponding wild-type enzyme (p. 20 at paragraph 18). This statement was made in distinguishing the instantly claimed mutant prenyl diphosphate synthase from those of the '725 and '909 patents. At p. 17 of the instant remarks, applicant disagrees with the examiner's assertion, noting that the claims are "silent, explicitly or implicitly, on any requirement of the mutant prenyl diphosphate syntase [sic] synthesizing prenyl diphosphate shorter than the prenyl diphosphate synthesized by the wild type enzyme."

The examiner acknowledges that the instantly claimed mutant prenyl diphosphate synthase of claim 1 is silent with respect the activity of the polypeptide. As noted above, the polypeptide of claim 1 encompasses mutants of SEQ ID NO:1 having *any* activity. However, as noted above, the mutant of claim 1 *as filed on 12/22/06* is limited to SEQ ID NO:1, except specifically recited mutations as set forth in lines 4-14 of claim 1, *i.e.,* SEQ ID NO:1, except the mutations of T78F and H81A; except the mutations of T78F and H81L; except the mutations of F77Y, T78F, and H81L; except the mutations of F77Y, T78F, and H81A; or except the mutations of F77Y, T78S, V80I, I84L, and 84PS85, which is undisputed by applicant. These specific mutants are shown in Figure 3 to produce a greater amount of farnesyl diphosphate relative to that of wild-type.

Conclusion

[17] Status of the claims:

- Claims 1-4, 6-7, 11-16, and 49-53 are pending.
- Claims 1-4, 6-7, 11-16, and 49-53 are rejected.
- No claim is in condition for allowance.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

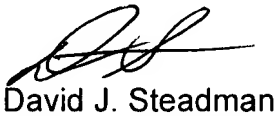
A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of

the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to David J. Steadman whose telephone number is 571-272-0942. The examiner can normally be reached on Mon to Fri, 7:30 am to 4:00 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Kathleen Kerr Bragdon can be reached on 571-272-0931. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).



David J. Steadman, Ph.D.
Primary Examiner
Art Unit 1656